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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/099,858	03/14/2002	Bonnie M. Davis	U 013913-4	4479

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EXAMINER	
SHARAREH, SHAHNAM J	

ART UNIT	PAPER NUMBER
1617	

DATE MAILED: 04/08/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/099,858	DAVIS, BONNIE M.	
	Examiner	Art Unit	
	Shahnam Sharareh	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *29 November 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 3-39* is/are pending in the application.

4a) Of the above claim(s) *5-36* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,4 and 37-39* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Amendment filed on November 29, 2004 has been filed. Applicant made the election of claims directed to the use of Galanthamine on February 04, 2004.. Claims 1, 3-4, 37-39 are directed to this species. Claims 5-36 stand withdrawn from further consideration as being drawn to a nonelected species. Any rejection that is not addressed in this Office Action is considered obviated in view of the claim amendments.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 3-4 and any dependent claims thereof are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention

The factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described in *In re Wands,* 8 USPQ2d 1400 (Fed. Cir. 1988). Among these factors are: (1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the

predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary. When the above factors are weighed, it is the examiner's position that one skilled in the art could not practice the invention without undue experimentation.

(1) The nature of the invention:

The invention provides for methods of treating any CNS function or cognitive performance caused by low LDL-cholesterol values in the brain by modulating nicotinic receptor using such drugs as nicotinic allosteric potentiators, acetylcholinesterase inhibitors et...

(2) The state of the prior art

The state of prior art for methods of treating the effects of low LDL-cholesterol values in brain on cognitive performance and CNS function by modulating nicotinic receptors has not been well described. In fact, the data described in the prior art are contradictory and inconclusive as to the pathophysiology and efficacy of drug therapy for such conditions. For example, the pathophysiology and drug treatment of Alzheimer disease (AD), one of the cognitive functions encompassed by the instant claims, have been inconclusive.

Furthermore, aside from the fact that the recitation of nicotinc allosteric potentiators, acetylcholinesteratse inhibitors etc.. is vague, there is no indication in the art that any such drugs can treat effects of low LDL-cholesterol values in the brain.

(3) The relative skill of those in the art

The relative skill of the those in the art is high, because it includes such persons competent in the field of pharmacology, neuropharmacology, clinical neurologists and even neuroradiologists or surgeons. One of ordinary skill in the art must possess competent knowledge in all such areas in order to interpret the efficacy, potency and toxicity associated with the claimed invention.

(4) The predictability or unpredictability of the art

The state of art in identifying patients with low LDL-cholesterol values in the brain, the effects of such levels on cognitive performance and other CNS functions, pathophysiology and clinical efficacy are quite unpredictable.

First, Examiner draws Applicant attention on the article authored by Jurevics et al (J. Neurochem, 1995; 64, 895-901) wherein Jurevics assessed the role of local synthesize of cholesterol in the brain and the contribution of serum cholesterol or diet in supplying cholesterol for myelination in brain. Accordingly, Jurevics concluded that

cholesterol accumulation in brain is a function of local synthesis and not associated with diet or ex-brain cholesterol production. (See abstract, pages 897-899, 900). Accordingly, determining the role of the serum LDL-cholesterol for monitoring or initiating any treatment of CNS disease is unpredictable.

Applicant's attention is also drawn to Simons et al (Neurology 2001; 57:1089-1093 of record), wherein Simon describes that the relationship between cholesterol levels and AD is merely speculative and hypothetical and requires further experimentation. (see page 1092, last 2 paragraphs). In fact, Simon describes Statins to reduce likelihood of developing AD by 60-73%. (see page 1091 2nd para.). Such speculations in the art are in direct opposition of the instantly described methodologies. Since, the publication of Simon is nearly the same as the filing date of the instant application, Examiner concludes that the state of art on the claimed subject matter is highly unpredictable and can only be determined on a case to case basis by conducting careful experimental studies.

(5) The breadth of the claims

The claims are very broad. The claims are directed to the methods of treating any cognitive performance or other CNS functions caused by low LDL-cholesterol values in the brain, without setting forth exactly the types of diseases or conditions to be protected. In fact, in order to ascertain the role of cholesterol on any impaired CNS function and further establish the entire genus of such diseases, one of ordinary skill in the art is required to perform in-depth i*n vitro* cellular assays and longitudinal human studies which are not construed to be routine.

(6) The amount of direction or guidance presented

The specification merely describes potential applicability of the instant methodologies without actual instruction. The specification and the state of art has enabled only for administration of drugs effecting nicotinic receptors in patients already receiving Statin therapy and a presumption of success. However, the specification provides no guidance, in the way written description, the etiology and pathophysiology of all CNS impairments caused by low brain LDL. Neither has specification provided any direct effects or therapeutic regimen for achieving the intended clinical outcome

A disclosure should contain representative examples which provide reasonable assurance to one skilled in the art that the compounds fall within the scope of a claim will possess the alleged activity. See *In re Riat et al.* (CCPA 1964) 327 F2d 685, 140 USPQ 471; *In re Barr et al.* (CCPA 1971) 444 F 2d 349, 151 USPQ 724. Here, there is no indication in the art or specification that the employed compounds can provide the biological activity claimed. Thus, the claimed biological activity cannot be predicted a prior art or disclosure and must be determined from a case to case painstaking experimental study.

(7) The presence or absence of working examples

As stated above, the specification discloses numerous potential therapeutic compounds without their actual effects on improving CNS or cognitive performance.

(8) The quantity of experimentation necessary

Since methods of ascertaining low-LDL brain cholesterol, establishing the relationship of such levels with CNS diseases (such as AD), determining potential patients, describing the role of systemic cholesterol levels and brain cholesterol, developing effective monitoring criteria, and attributing the effects to drug therapy, cannot be predicted, one of ordinary skill in the art must perform careful experimental studies to practice the instantly claimed invention. Accordingly, when the above enumerated factors are weighed together, one of ordinary skill in the art would be burdened with undue "painstaking experimentation studies" to practice the claimed invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 3-4, 37-39 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claims 1 and 37 respectively, the recitations of "treating the effects of low LDL-cholesterol values in the brain on cognitive performance or other central nervous system functions," "modulating nicotinic receptors," and "nicotinic allosteric potentiators" render the claims ambiguous. it is not clear to which conditions is applicant refereeing, which type of effects is applicant looking for and what type of drugs are viewed to potentiate nicotinic allosteric response. The specification fails to describe the metes and bounds of such claims. Accordingly, clarification is requested.

Claim 1 recites "the effects of low LDL-cholesterol values in the brain;" however, the body of claim requires determination of LDL-cholesterol level of below 109 mg/dl. It is not clear whether, such measurement is a serum cholesterol level or brain cholesterol

levels. Accordingly, it is not clear how to identify patients in need of the claimed treatment.

Claim Rejections - 35 USC § 103

Claims 37-39 are rejected under 35 U.S.C. 103(a) as being unpatentable over Davis, Kvipelto et al, (BMJ, Vol 322, 16 June 2001) and Simons et al, (Neurology 2001;57:1089-1093).

Applicant's arguments with respect to this rejection have been fully considered but are not found persuasive. Applicant argues that there is no motivation in the art to combine the references, because such combination provide a different intended benefit as the claimed invention. (see Remarks at page 9, para. 3).

In response Examiner states that the fact that applicant has recognized another advantage which would flow naturally from following the suggestion of the prior art cannot be the basis for patentability when the differences would otherwise be obvious. See *Ex parte Obiaya*, 227 USPQ 58, 60 (Bd. Pat. App. & Inter. 1985).

Here, the claims are directed to methods of improving cognitive disease of patients who are receiving Statin therapy by administering galanthamine.

Examiner has reasoned that any elderly patient that receives statings for hyperlipidemia and Galanthamine for their Alzheimer would meet the process steps of the instant claims.

. Davis teaches the use of Galanthamine for treating Alzheimer which is a disease associated with advance of age and increase level of cholesterol.

Kivipelto showed that advancing age leads to increase cholesterol concentrations, which eventually leads to higher risk of Alzheimer disease. Kivipelto in table 2, and para 1 and 2 of page 1449 describes that high cholesterol concentrations are significant risk factors for Alzheimer's disease.

Simons show that at least in risk of developing Alzheimer is lower in patients that receive Statins for treating hyperlipidemia. (see Simon at pages 1091-1092). The use of Statins at clinically significant levels of cholesterol values is well within the level of ordinary skill in the art. Simon already attests that there are studies wherein patients with AD are also receiving statins.

Accordingly, based on Kivipelto and Simons Statins are not only useful for treating high cholesterol but also for lowering the risk of patients at risk to develop Alzheimer.

Thus, Examiner concluded at least it would flow naturally from following the suggestion of the prior art to add to the drug regimen of elderly patients who suffer from Alzheimer and are already receiving statins for their hyperlipidemia, as described by Simon and suggested by Kivipelto, sufficient doses of galanthamine to improve cognitive behavior, because as described by Davis, the ordinary skill in the art would have had a reasonable expectation of success in observing improvement of their Alzheimer.

Furthermore, Applicant has not provided any evidence showing the criticality of cholesterol levels at a range of 109 mg/dl. Accordingly, identifying suitable patients by

routinely observing their cholesterol levels during a course of hyperlipidimic treatment would have been achievable by routine experimentations.

Conclusion

No claims are allowed at this time.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Shahnam Sharareh whose telephone number is 571-272-0630. The examiner can normally be reached on 8:30 am - 6:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreenivasan Padmanabhan, PhD can be reached on 571-272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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SREENI PADMANABHAN
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